Effect of Steroids Therapy on Serum levels of Anticardiolipin Antibodies (IgG) in Children and Adolescents with Intractable Epilepsy

Thesis
Submitted for Partial Fulfillment of Master Degree in
Pediatrics

By
Ola Mohamed Ibrahiem Seliem
(M.B.B.CH., 2004) Ain-Shams University

Under supervision of

Dr. Omnia Fathy El-Rashiedy

Professor of Pediatrics
Faculty of Medicine – Ain Shams University

Dr. Rasha Hussien Aly

Assist. Professor of Pediatrics Faculty of Medicine – Ain Shams University

Dr. Rania Hamdy El Kabariti

Lecturer of Clinical Pathology Faculty of Medicine – Ain Shams University

> Faculty of medicine Ain-Shams University 2010

تأثير تعاطي عقار الكورتيزون علي نسبة الاجسام المضاده للكار ديوليبين (النوع جـ) في المرضي المصابين بالصرع المستعصي العلاج

رسالة توطئه للحصول علي درجة الماجستير في طب الأطفال

مقدمه من

علا محمد إبراهيم سليم بكالوريوس الطب و را (2004)

تحت إشراف الدكتورة / أمنية فتحى الرشيدي

.

الدكتورة / رشاحسين علي

<u>ب</u>

_ <u>.</u>

الدكتورة / رانيا حمدي الكباريتي

مدرس الباثولوجيا الاكلينيكية

كلية الطب جامعة عين شمس 2010

acknowledgements

First and foremast thanks are to Allah, the most kind and merciful.

I would like to express my deepest thanks and profound gratitude to **Prof. Dr. Omnia Fathy El-Rashiedy**, Professor of Pediatrics, Faculty of Medicine, Ain Shams University. It was great pleasure to work under her kind guidance and her continuous help combined with her sincere support.

I am really indebted and greatly honored to express my extreme thankfulness to **Dr. Rasha Hussien Aly**, Assistant Professor of Pediatrics, Faculty of Medicine, Ain Shams University, for her valuable supervision of my thesis, her unlimited support and simulative encouragement throughout the work.

I am also most grateful to **Dr. Rania Hamdy El Kabariti**, Lecturer of Clinical Pathology, Faculty of Medicine, Ain Shams University for her great help in the laboratory aspect of this work.

Finally, I would like to convey my warmest gratitude to my family, my professors in department of Pediatrics, my colleagues, my patients and their families and nursing staff of pediatric neurology clinic, and epilepsy clinic of neurology department, Ain Shams University.

Ola Mohamed Ibrahiem Seliem

CONTENTS

| | Page |
|----------------------|------|
| Introduction | 1 |
| Aim of the Work | 3 |
| Review of Literature | 4 |

| Epilepsy | 4 |
|--|-----|
| Intractable epilepsy | 42 |
| Cardiolipin | 48 |
| Anti-CardioLipin antibodies | 59 |
| Corticosteroids | 64 |
| Subjects and Methods | 79 |
| Results | 87 |
| Discussion | 120 |
| Summary | 138 |
| Recommendations | 142 |
| References | 143 |
| Appendices | |
| Arabic Summary | |
| | |
| LIST OF TABLES OF REVIEW OF LITERATURE | |

| Table No. | Title | Page |
|-----------|---|------|
| 1 | Cause of seizures | 7 |
| 2 | Drugs associated with epileptic seizures | 8 |
| 3 | Factors which may precipitate seizures in susceptible individuals | 9 |

| 4 | ILAE classification of epileptic seizures | |
|----|---|----|
| 5 | Classification of absence seizures | 15 |
| 6 | The ILAE classification of epileptic syndromes (1989) | 19 |
| 7 | How can EEG help in epilepsy? | 28 |
| 8 | Guidelines for specific seizure types and epilepsy syndromes | 30 |
| 9 | Common AEDs | 35 |
| 10 | Common AEDs Cont. | 36 |
| 11 | Individual steroids ratio between mineralo and glucocorticoid actions | 67 |

LIST OF TABLES OF RESULTS

| Tab No | | Page |
|-----------|--|------|
| 1 | Causes and time of dropping out from the study | 88 |
| 2 | Age distribution among patients and controls | 88 |
| 3 | Sex distribution among patients and controls | 89 |
| 4 | Comparison between patients and controls as | |
| | regards anthropometric measurements | 89 |
| 5 | Comparison between patients and controls as | |
| | regards serum levels of Anti-Cardiolipin | |
| | antibodies (aCL-ab) | 90 |
| 6 | Personal data of the epileptic patient's group | 92 |
| 7 | Classifications' data of the epileptic patient's group | 93 |
| 8 | Seizures frequency and severity data | 94 |
| 9 | Electro-encephalographic data | 95 |
| 10 | Serum levels of Anti-Cardiolipin antibodies (aCL- | -ab |
| | IgG) of the patient's group | 96 |
| 11 | The number of antiepileptic drugs | 96 |
| 12 | The Types of antiepileptic drugs | 97 |
| 13 | Symptomatic generalized Epilepsies | 98 |
| 14 | Lennox-Gastaut syndrome patients | 100 |
| 15 | Parietal lobe epilepsies patients | 102 |

LIST OF TABLES OF RESULTS (Cont.)

| Table No. | Title | Page |
|-----------|--|---------------|
| 16 U | ndetermined generalized epilepsies patients | 104 |
| 17.Te | emporal lobe epilepsy patient | 106 |
| 18 R | asmussen Encephalitis patient | 107 |
| 19 Tl | he myoclonic astatic epilepsy patient | 109 |
| 20 dy | verse effects of steroids reported in patients | 110 |
| | hanges of seizures' frequency of patients alou | ng the 111 |
| | hanges of Chalfont severity score of patients ong the study | 112 |
| | hange of EEG recordings of patients along the udy | 114 |
| | hanges of Anti-Cardiolipin antibodies Serum vels of patients along the study | 114 |
| | ffect of steroids on clinical data of patients' ecording to aCL-ab positivity. | 116 |
| | ffect of steroids on neurophysiological data of attients' according to aCL-ab positivity | 116 |
| | ffect of steroids on clinical data of patients' ecording to seizures' types | 117 |
| | ffect of steroids on neurophysiological data of atients' according to seizures' types | 117 |
| | ffect of steroids on clinical data of patients' cording to epilepsy types | 118 |
| | ffect of steroids on neurophysiological data of attents' according to epilepsy types | 118 |

| 31 | Correlations of serum levels of Anti-Cardiolipin | |
|----|--|-----|
| | antibodies (aCL-ab IgG) and seizures' description data | 119 |
| 32 | Correlations of serum levels of Anti-Cardiolipin | 119 |
| | antibodies (aCL-ab IgG)and AEDs' doses and durations before steroids therapy | 119 |
| | | |

LIST OF FIGURES OF REVIEW OF LITERATURE

| Figure | re Title | |
|--------|--|----|
| No. | | |
| 1 | Structure of Cardiolipin | 48 |
| 2 | Metabolism of Cardiolipin (Eukaryotic pathway) | 51 |
| 3 | Metabolism of Cardiolipin (prokaryotic pathway) | 52 |
| 4 | Respiratory electron transfer of Complex IV | 53 |
| 5 | Mechanism of how CL trigger apotosis | 54 |
| 6 | How Cardiolipin serves as a proton trap in oxidative phosphorylation | 55 |
| 7 | structure of Corticosterone | 64 |
| 8 | Corticosteroid biosynthetic pathway | 65 |
| | LIST OF FIGURES OF RESULTS | |

| | Figure Title No. | |
|---|--|-----|
| | | |
| 1 | aCL-ab (IgG) levels in patients and controls | 90 |
| 2 | aCL-ab (IgG) positivity in studied group | 91 |
| 3 | Changes of seizures' frequency of patients along | |
| | the study | 111 |
| 4 | Changes of Chalfont severity score of patients | |
| | along the study | 113 |
| 5 | aCL-ab (IgG) levels in patients before and after | |
| | steroid therapy | 115 |
| 6 | aCL-ab (IgG) positivity in patients before and after | |
| | steroid therapy | 115 |

List of Abbreviations

aCL-ab Anti-Cardiolipin antibodies ACTH Adrenocarticotrophic hormone

ADHD Attention-deficit/hyperactivity disorder

AEDS Antiepileptic Drugs ALT Alanine transaminase

aPL-Ab Anti phospholipid antibodies
APS Antiphospholipid syndrome
AST Aspartate transaminase
ATP Adenosine triphosphate
B2GP 1 Beta 2 glycoprotein 1
BOE Benign occipital epilepsy

Ca⁺⁺ calcium

CAE Childhood Absence Epilepsy

CBC Complete blood count

CDP-DAG Cytidinediphosphate-diacylglycerol

Cl Chloride
CL Cardiolipin

CLS Cardiolipin synthase
CNS Central Nervous system
CPS Complex partial seizures

CRH Corticotropin-releasing hormone

CS Corticosteroids

CSF Cerebro Spinal Fluid

CT scan Computerized tomography scan

ECSWS Epilepsy with continuous spike waves during slow-

wave sleep

EEG Electro Encephalography

ELISA Enzyme-linked immunosorbent assay

Éar, nose and throat

FDA Food and drugs administration

FMRI Functional MRI

GABA Gamma Amino Butyric Acid

GABRA1 alpha 1 subunit of GABA-A receptor

GAD Glutamic acid decarboxylase

GCA Giant cell arteritis
GLUR3 Glutamate receptor 3

List of Abbreviations (Cont.)

GSW Generalized spike wave GTC Generalized Tonic colonic

IE Intractable epilepsy

IED Interictal epileptiform discharge

IgA Immunoglobulin A

IGE Idiopathic generalized epilepsy

IgG Immunoglobulin G IgM Immunoglobulin M

ILAE International League Against Epilepsy

IS Infantile spasm

IvIgs Intravenous immunoglobulins
JAE Juvenile Absence Epilepsy
JME Juvenile myoclonic epilepsy

K⁺ Potassium

LGS Lennox Gastaut syndrome
LKS Landeu-kleffner syndrome
MDR-1 Multiple drug resistance gene

Mg⁺⁺ Magnesium

MRI Magnetic resonant Imaging

MRS Magnetic resonance spectroscopy

MS Multiple sclerosis

MTLE Mesial temporal lobe epilepsy

Na⁺ Sodium

NAO Nonyl acridine orange PA phosphatidic acid

PET Proton emission tomography
PGP Phosphatidylglycero phosphate

PLA phospholipase A2
PLD Phospholipase D
PLP Pyridoxal-5-phosphate
PMR Polymyalgia rheumatica

RE Rasmussen's encephalitis SD Standard deviation

SIADH Syndrome of inappropriate secretion of antidiuretic

hormone

SLE systemic lupus erythematosus

SPET Single photon emission computerized tomography

List of Abbreviations (Cont.)

SPS Simple partial Seizures

SUDEP Sudden unexpected death in epilepsy

TLE Temporal lobe epilepsy VNS Vagus nerve stimulation

 $\begin{array}{ll} VPA & Sodium\ valproate \\ WS & West\ syndrome \\ \chi^2 & Chi\text{-square\ test} \end{array}$

Appendix 1

Questionnaire

Personal History

- Serial No:
- Age:
- Sex: -male -femaleConsangunity: +ve -ve

Seizure History

- A. Seizure Description
- Age of onset:
- Last seizure occured on:



| су |
|----|
| |

| • | Post Ictal stupor | -Yes | -No |
|---|-------------------|------|-----|
| • | Aura | -Yes | -No |

PPT Factors

Loss of consciousness-Yes-NoEnuresis-Yes-No

B. Drugs

Drug 1

Name:

| • | Dose: | ml/kg/day |
|---|-----------|-----------|
| • | Duration: | /month |

Drug 2

Name:

Dose: ml/kg/dayDuration: /month

Drug 3

■ Name:

Dose: ml/kg/dayDuration: /month

Drug 4

Name:

Dose: ml/kg/dayDuration: /month

| C. Chalfont severity scale | C. | Chalfont | severity | scale |
|----------------------------|----|----------|----------|-------|
|----------------------------|----|----------|----------|-------|

| Loss of awareness: | no=0, $yes=1$ |
|--|----------------|
| • Warning (if loss of awareness): | no=1,yes=0 |
| • Drop/Spill a held object: | no=0,yes=1 |
| • Fall to the ground: | no=0,yes=4 |
| • Injury: | no=0, yes=20 |
| • Incontinence: | no=0,yes=8 |
| • Automatism: | no=0 |
| | Mild=4 |
| | Severe=12 |
| • Convulsion: | no=0,yes=12 |
| • Duration of seizure: | <10 sec = 0 |
| | $< 1 \min = 1$ |
| | 1-10 min=4 |
| | >10 min=16 |
| Time to return to normal from onset: | $< 1 \min = o$ |
| | $1-10\min = 5$ |
| | 10-30min=20 |
| | 3o-60min=30 |
| | 1-3hr = 50 |
| | >3hr = 1oo |
| If seizure event with total score | =0,add 1 |

If seizure event with total score If only in sleep, divide score by 2

In each section, score what usually occurs with fractionation as follow:

- No score if it does not occur ,quarter of score if occurs in up to 25% of attacks.
- Half score if occurs in 25-50% of attacks, three quarters if in 50-75%
- Full score if occurs in >75% of attacks

Injury includes tongue bitting, laceration and bruising Spill includes a held object even if the vessel is not dropped Convulsions is taken to mean clonic jerking of the limbs

Past History

1. Anti natal history

| Maternal fever | -Yes | -No |
|--|------|-----|
| Maternal Rash | -Yes | -No |
| Chronic diseases | -Yes | -No |
| Placental seperation | -Yes | -No |
| Pre-eclampsia | -Yes | -No |
| Fetal distress | -Yes | -No |

2. Natal History

| • | Place of birth | -Hospital | -Home |
|---|------------------|-----------|-------|
| • | Type of delivery | -Noramal | -C.S |
| • | Preterm labor | -Yes | -No |
| • | Obstructed labor | -Yes | -No |

| 3. Post natal history | | |
|--|--------------|-------------|
| Cry | -Immediate | -Delayed |
| Cyanosis | -Yes | -No |
| Developmental History | | |
| Speech | -Yes | -No |
| Sphincter | -Yes | -No |
| Motor | -Yes | -No |
| Vaccination | | |
| Appropriate | | |
| Inappropriate | | |
| Family History | | |
| Order of birth | | |
| Family history of epilepsy | -Yes | -No |
| Family history of heredofamilial | disease -Yes | -No |
| Examination | | |
| Neurological Examination | | |
| Orientation | | |
| Mentality | | |
| Gait | | |
| Cranial nerves | | |
| Sensory examination | | |
| Motor examination | | |
| Coordination | | |
| General Examination | | |
| Weight: | | kg |
| Height: | | cm |
| Head Circumference: | | cm |
| Blood pressure | | |
| Temperature | | |
| Respiratory rate | | |
| Investigation | | |
| 1-EEG report: | | |
| 2-CT,MRI report: | | |
| 3-Serum level of aCL-ab: | | |
| Steriod Therapy | | |
| Onset: | | |
| ■ Dose: | | Total Dose: |
| Start of tapering: | | |
| • Stop: | | |
| • Adverse effect encountered: | | |
| Post therapy assessment | | |
| 1-Seizure Frequency | | |
| 2-Chalfont Severity Scale | | |
| 3-EEG report | | |
| 4- Serum level of aCL-ab | | |
| | | |